PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 100894-1 WO	**FOR FURTHER ACTION** See Form PCT/IPEA/416	
International application No. PCT/SE2003/001712	International filing date *(day/month/year)* 06.11.2003	Priority date *(day/month/year)* 07.11.2002
International Patent Classification (IPC) or national classification and IPC C07D 277/22,277/24,277/26,277/28,417/12, A61K 31/426, A61P 29/00,19/02,9/00,25/06,25/08,25/18,35/00,37/08,1/00,31/12		
Applicant AstraZeneca AB et al		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *(sent to the applicant and to the International Bureau)* a total of _____ sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))
      _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the report
   - ☒ Box No. II Priority
   - ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☒ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☒ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
18.05.2004	15.02.2005
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Form PCT/IPEA/409 (cover sheet) (January 2004)

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/SE2003/001712

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of:

☐ international search (under Rules 12.3 and 23.1(b))
☐ publication of the international application (under Rule 12.4)
☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

☒ the international application as originally filed/furnished

☐ the description:

pages _____ as originally filed/furnished
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☐ the claims:

pages _____ as originally filed/furnished
pages* _____ as amended (together with any statement) under Article 19
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☐ the drawings:

pages _____ as originally filed/furnished
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/figs _____
☐ the sequence listing *(specify)*: _____
☐ any table(s) related to the sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/figs _____
☐ the sequence listing *(specify)*: _____
☐ any table(s) related to the sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

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Box No. II Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

   ☐ copy of the earlier application whose priority has been claimed (Rule 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 66.7(b)).

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1). Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

The priority is considered valid. Therefore, the document in Box No. VI is of no relevance for this report.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 15-17

because:

☒ the said international application, or the said claims Nos. 15-17 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

See PCT Rule 67.1.(iv).: Methods for treatment of the human or animal body by therapy, as well as diagnostic methods.

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____ are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in the Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

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Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-14, 18	YES
	Claims	-	NO
Inventive step (IS)	Claims	-	YES
	Claims	1-14, 18	NO
Industrial applicability (IA)	Claims	1-14, 18	YES
	Claims	-	NO

2. Citations and explanations (Rule 70.7)

Reference is made to the following documents:

D1: WO0162704 (closest prior art)
D2: WO0162713 (cited only as an example of the prior art)
D3: WO0162714 (cited only as an example of the prior art)
D4: WO0162721 (cited only as an example of the prior art)

D1 (Example 53, pages 63-65; Example 79, pages 95-97; page 5, line 19 - page 9, line 8; page 25, line 13 - page 28, line 10; the claims), representing the closest prior art, describes analogues of the compounds in the present application, known as inhibitors of nitric oxide synthase (NOS), especially of inducible NOS (iNOS), with use in the treatment of the same NOS-/iNOS-related diseases as the ones preferred in the present application.

The compounds claimed in the present application differ from the compounds in D1 in that they have a thioether bridge instead of an ether bridge and in that they have a hydroxymethyl group in the alpha position.

The problem to be solved through the difference between the compounds of the application and the compounds in D1 can be said to be the providing of alternative medicaments for use in the treatment of the above mentioned disorders.

The exchange of -S- for -O- in the ether bridge is considered to be a standard alternative for the person skilled in the art, and analogues of the compounds in the application having this substitution, and the same properties and use, can be found in the documents D2-D4.

.../...

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Box No. V

The compounds in the present application are substituted α-methylpropylamines, or sec-butyl amines. D2 describes analogues that are n-butyl amines, i.e. the alkyl chain between -S- and -NH2 is butylene instead of propylene; see the claims and Example 43, pages 62-64, in which W is 2-thiazolyl as in the present application. Since it is known from the prior art that the activity of the compounds is retained when the alkyl chain between S/O and -NH2 is changed from propylene (as in D1) to butylene (as in D2), α-methylpropylene derivatives would be considered an obvious alternative to the person skilled in the art.

Accordingly, the relevant difference between the compounds of the present application and the compounds of the prior art is the presence of an α-hydroxymethyl group. However, since the production of new analogues of pharmaceutical compounds is today common practise, this derivatisation can not in itself be considered enough to justify an inventive step. For an inventive step to be considered to prevail, it has to be shown with comparative examples that the compounds of the present application have an unexpected and beneficial technical effect compared to the compounds of the closest prior art, i.e. the compounds in D1. In the absence of such proof, the invention according to claims 1-14 and 18 has to be considered to lack an inventive step.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
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Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

Application No. Patent No.	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date (valid claim) *(day/month/year)*
WO02090332	14.11.2002	06.05.2002	08.05.2001 28.09.2001

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure *(day/month/year)*	Date of written disclosure referring to non-written disclosure *(day/month/year)*

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The expressions relating to inhibition of nitric oxide synthase activity and the expressions relating to inflammatory diseases in claims 7-9 and 14-17 relate to a large number of different disorders which cannot be clearly defined by these expressions. The application provides support for use of the compounds in the treatment of only a very limited number of such disorders. Moreover, the pharmacological effect inhibition of nitric oxide synthase activity cannot in itself be regarded as a therapeutic application. There are an undefined number of diseases which might be related to this pharmacological effect. A practical application still needs to be found in the form of a defined treatment of a specified pathological condition, this being an essential technical feature, in order to render claims 7-9 and 14-17 clear. Claims 7-9 and 14-17 do therefore not meet the requirements of Article 6 PCT that claims shall be clear, concise and suported by the description.